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TI - FK960, a novel potential anti-dementia drug, augments long-term potentiation in mossy fiber-CA3 pathway of guinea-pig hippocampal slices.
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AB - Our previous studies have demonstrated that FK960 (FR59960; N-(4-acetyl-1-piperazinyl)-p-fluorobenzamide monohydrate), a novel antidementia piperazine derivative, exerts beneficial effects on memory deficits in various animal models of amnesia in rats (M. Yamazaki, N. Matsuoka, N. Maeda, Y. Ohkubo, I. Yamaguchi, FK960 N-(4-acetyl-1-piperazinyl)-p-fluorobenzamide monohydrate ameliorates the memory deficits in rats through a novel mechanism of action, J. Pharmacol. Exp. Ther., 279 (1996) 1157-1173.) and in rhesus monkeys (N. Matsuoka, T.G. Aigner, FK960 (N-(4-acetyl-1-piperazinyl)-p-fluoro benzamide monohydratel, a novel potential antidementia drug, improves visual recognition memory in rhesus monkeys: comparison with physostigmine, J. Pharmacol. Exp. Ther., 280 (1997) 1201-1209). To clarify the synaptic mechanisms of its antiamnesic action, FK960 was investigated for its effects on the development of long-term potentiation (LTP) in guinea-pig hippocampal slices. The magnitude of LTP of population spike recorded in CA3 pyramidal neurons was significantly augmented by perfusing FK960 (10-9-10-6 M) for 25 min before and during tetanic stimulation of the mossy fibers, whereas the basal amplitude of population spikes before tetanus was hardly affected by the drug. The dose-response curve was bell-shaped with a maximal augmentation at 10-7 M. Scopolamine (10-6 M) per se had little effect on the magnitude of LTP in the mossy fiber-CA3 pathway, but significantly attenuated its enhancement by FK960 (10-7 M). In hippocampal slices from animals treated with cysteamine (200 mg/kg, s.c.), which was shown to deplete the hippocampal somatostatin, FK960 (10-7 M) hardly affected the LTP. These results suggest that FK960 enhances the magnitude of LTP in the mossy fiber-CA3 pathway through an activation of the cholinergic-somatostatinergic link in the hippocampal formation. Furthermore, it can be postulated that the drug regulates the cognitive function by modulating directly synaptic plasticity in the hippocampal neuronal network.